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Research article

Association of dynamic changes in arterial partial pressure of carbon dioxide with neurological outcomes in aneurysmal subarachnoid hemorrhage

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ABSTRACT

Background: Cerebral blood flow (CBF) is closely regulated by carbon dioxide (CO_2). In patients with aneurysmal subarachnoid hemorrhage (aSAH), abnormal arterial partial pressure of CO_2 ($PaCO_2$) might deteriorate brain injuries. Nevertheless, the impact of dynamic $PaCO_2$ fluctuations on neurological outcomes in aSAH patients has not been extensively studied. Our study aimed to investigate the association between dynamic $PaCO_2$ levels and unfavorable neurological outcomes in aSAH patients.

Methods: In this retrospective observational study, we consecutively enrolled 159 aSAH patients from December 2019 to July 2021. Arterial blood gas measurements within 10 days after intensive care unit (ICU) admission for each patient were recorded to calculate the time-weighted average (TWA)-$PaCO_2$, an indicator representing the dynamic changes in $PaCO_2$ levels. For the association between TWA-$PaCO_2$ levels and unfavorable neurological outcomes in aSAH patients, multivariable logistic analysis was used to explore TWA-$PaCO_2$ levels as categorical variables, and restricted cubic spline (RCS) was used to explore TWA-$PaCO_2$ levels as continuous variables.

Results: In multivariable logistic analysis, after adjusting confounders, when TWA-$PaCO_2$ 35–45 mmHg was as a reference, TWA-$PaCO_2$ < 35 mmHg (odds ratio [OR] 2.15, 95 % confidence interval [CI] 0.83–5.55, P = 0.113) and TWA-$PaCO_2$ > 45 mmHg (OR 8.31, 95 % CI 0.72–96.14, P = 0.090) were not independently associated with unfavorable neurological outcomes (modified Rankin score of 3–6). The RCS shows a "U" shape curve between TWA-$PaCO_2$ levels and unfavorable neurological outcomes, with a nonlinear P-value of 0.023. The lowest ORs of unfavorable neurological outcomes were within $PaCO_2$ 32.8–38.1 mmHg.

Conclusions: Both lower and higher $PaCO_2$ levels are harmful to aSAH patients. $PaCO_2$ in the range of 32.8–38.1 mmHg is associated with lowest unfavorable neurological outcomes.

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1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a particularly devastating cerebrovascular event [1]. Neurological impairment and cognitive dysfunction after aSAH remain high and affect relatively young patients at their most productive years in life [2]. Patients with aSAH typically suffer from compromised cerebral perfusion and metabolism, under which circumstances, a dramatic reduction in cerebral blood flow (CBF) triggered by the decrease in arterial partial pressure of arterial carbon dioxide ($PaCO_2$) [3] or elevated intracranial pressure (ICP) due to the increase in $PaCO_2$ [4] would produce additional attacks on the injured brain [5].

Studies have shown that derangements of $PaCO_2$ jeopardize cerebral perfusion and aggravate brain metabolic crises and potential neurological injury in patients with brain injury [6–9]. Nevertheless, in previous studies, there was a notable variation in the threshold values for $PaCO_2$ levels used to identify hypocapnia or hypercapnia. $PaCO_2$ less than 25 mmHg–35 mmHg was the range for hypocapnia, while $PaCO_2$ higher than 45 mmHg–50 mmHg was the range for hypercapnia. In addition, the timepoint of $PaCO_2$ measurement also varied, from one measurement at admission to multiple measurements at any time during the hospital stay, mainly during the first ten days following cerebral injury [10]. Prior publications usually regard one outlier of $PaCO_2$ value at any time as abnormal. However, $PaCO_2$ levels are easily influenced by clinical scenarios, such as fever, pain, and inadequate sedation. The effect of dynamic $PaCO_2$ fluctuations on neurological outcomes in aSAH patients has not been well investigated.

Therefore, this study aims to explore the effect of dynamic carbon dioxide (CO_2) exposure on neurological outcomes in SAH patients and to describe the optimal $PaCO_2$ range that might benefit SAH patients.

2. Materials and methods

2.1. Study design

This was a single-center, retrospective, observational study conducted at the intensive care unit (ICU) of Beijing Tiantan Hospital. The study was reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated with Capital Medical University (KY2022-143-01). The study report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [11].

2.2. Study population

All patients diagnosed with aSAH admitted to the ICU between December 2019 and July 2021 were screened retrospectively and recruited consecutively. Only the data from the first admission was included for patients with multiple ICU admissions.

2.3. Inclusion and exclusion criteria

The study included adult patients (≥18) whose first diagnosis was "aSAH" confirmed by computed tomography (CT) angiography, digital subtraction angiography, or catheter angiography, and the patients were accepted for neurosurgical clipping within 24 h of hospital admission. Exclusion criteria were as follows: traumatic SAH or arteriovenous malformation, acceptance of endovascular coiling or conservative treatment, an interval longer than 24 h between the end of the surgery and ICU admission, arterial blood gas (ABG) measurements during ICU therapy were unavailable, pregnancy or lactating women, acute respiratory distress syndrome (because a low tidal volume, permissive hypercapnia ventilation strategy was usually performed), brain death (for better controlling

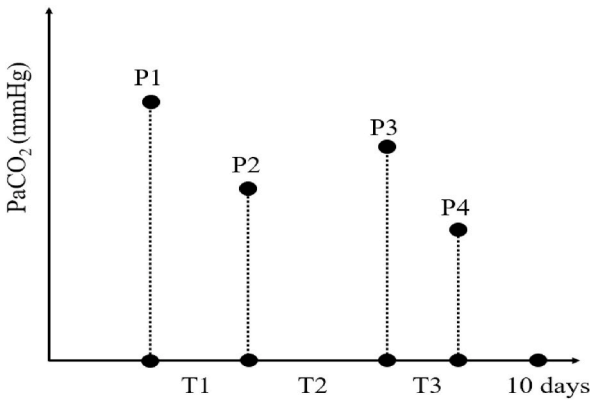

Fig. 1. The methods for calculation of TWA-$PaCO_2$. If the patient had 4 ABG measurements within 10 days after ICU admission, and the period between each two $PaCO_2$ measurements varied. The calculation formula was as follows: $\left(\left(\frac{P1+P2}{2}\right) \times T1 + \left(\frac{P2+P3}{2}\right) \times T2 + \left(\frac{P3+P4}{2}\right) \times T3\right) \div (T1 + T2 + T3)$.

the disease severity heterogeneity).

2.4. Data collection

The data included CO_2 exposure, baseline characteristics, aneurysm data, ICU therapy data obtained from electronic medical records, neuroimaging, and neuroradiology reports. The neurological outcome at 3 months based on the modified Rankin scale (mRs) was obtained from the neurosurgery's regularly scheduled aneurysm outpatient follow-up records by investigators unknown the patient's CO_2 exposure level. In case patients were not attended, the mRs score was assessed by investigators anonymized to the CO_2 exposure via telephone interview.

2.4.1. CO_2 exposure

The primary interest in CO_2 exposure was dynamic CO_2 changes, represented as time-weighted average-arterial partial pressure of carbon dioxide (TWA-$PaCO_2$). The values were obtained from all available arterial blood gas analysis measurements within each patient's initial ten days of ICU admission. The calculation method has been described by Nichol et al. [12]: the mean value of $PaCO_2$ values at two consecutive time points was multiplied by the period between respective time points firstly, then summed the mean values, which the obtained values divided by the total time (Fig. 1).

2.4.2. Baseline characteristics

Including 1) Demographic data (age, sex, body mass index (BMI)); 2) Medical history (history of hypertension, diabetes, cardiovascular disease); 3) Personal history (tobacco use, alcohol use); 4) Time from onset to hospital admission.

2.4.3. Aneurysm data

Including 1) Aneurysm characteristics (multiple or single, site and lateral of responsible aneurysm); 2) Hunt-Hess grade ascertained according to the clinical presentation at admission; 3) Modified Fisher scale determined by the amount of blood seen at initial CT scan.

2.4.4. ICU therapy data

Including primary clinical treatment (mechanical ventilation, opioids [including remifentanil and fentanyl]).

2.4.5. Outcomes

The primary outcome was the neurological outcome based on the mRs at 3 months, which ranges from 0 to 6, with 0 representing no symptoms and 6 representing deaths. An unfavorable outcome was defined as an mRs score of 3–6, and a favorable outcome was defined as an mRs score of 0–2.

2.5. Statistical analysis

Continuous variables with normal distribution were shown as mean and standard deviation (SD) and compared with Student t-tests. Continuous variables with skewed distribution were shown as median and interquartile range (IQR) and compared with Wilcoxon rank sum test. Categorical variables were shown as frequency and percentages (%) and compared with chi-square test.

Comparisons were made between groups according to unfavorable and favorable outcomes. The variables with statistically

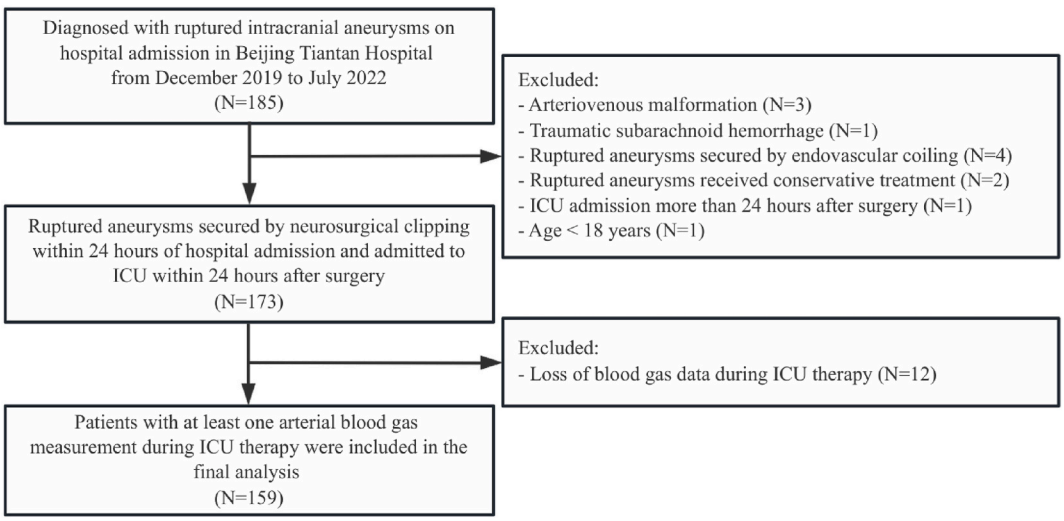

Fig. 2. The flow chart for patient screening.

significant ($P < 0.05$) were included in multivariate logistic regression analysis to calculate the adjusted odds ratios (ORs) and 95 % confidence intervals (CIs) for CO_2 exposure indicators. We also performed a restricted cubic spline (RCS) with three knots, adjusted for confounders [13] to show the possible nonlinear relationship between TWA-$PaCO_2$ levels as a continuous variable and unfavorable neurological outcomes.

All variables in our study were complete except for BMI (11.3 % missing, 18 in 159). To minimize bias caused by missing data, we applied mean value imputation to fill the data. Two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (version 26.0; IBM) and R software (version 4.1.2, www.r-project.org).

3. Results

3.1. Flow chart for enrollment and baseline characteristics

The flow chart for patient screening is shown in Fig. 2. In the time window for screening, 185 patients diagnosed with "aSAH" were admitted to the ICU, 26 patients were excluded according to the exclusion criteria, and 159 patients were included in the final analysis.

Clinical characteristics for 159 patients are shown in Table 1. 49 patients suffered from unfavorable neurological outcomes (defined as an mRs score of 3–6). The mean age was significantly higher in the unfavorable neurological outcomes group compared with the favorable outcome group (57.7 vs. 50.8, $P < 0.001$). A significantly higher proportion of Hunt-Hess grade 3–5 (69.4 % vs. 31.8 %, $P < 0.001$) and modified Fisher scale 3–4 (83.7 % vs. 51.8 %, $P < 0.001$) in the unfavorable neurological outcomes group. As for ICU therapies, there was more use of opioids (61.2 % vs. 36.4 %, $P = 0.004$) and mechanical ventilation (69.4 % vs. 17.3 %, $P < 0.001$) in the unfavorable outcomes group.

TWA-$PaCO_2$ values were shown as categorical variables and compared between the unfavorable and favorable outcomes groups. When TWA-$PaCO_2$ levels were categorized into three ranges: <35, 35–45, and >45 mmHg, there were higher proportions of TWA-$PaCO_2$ < 35 mmHg (51.0 % vs. 42.7 %) and lower proportions of TWA-$PaCO_2$ 35–45 mmHg (40.8 % vs. 56.4 %) in unfavorable outcome group compared with favorable outcome group, the sample of TWA-$PaCO_2$ > 45 mmHg was small. The overall difference in P value was 0.024. There were no significant differences in other variables.

3.2. Multivariate logistic regression analysis for unfavorable neurological outcomes

The variables that show significant differences between unfavorable and favorable outcomes groups were included in multivariate logistic regression analysis: age, Hunt-Hess grade, modified Fisher scale, opioids, mechanical ventilation, and TWA-$PaCO_2$ levels (Table 2). Based on multivariate logistic regression analysis, after adjusting the confounders, when TWA-$PaCO_2$ 35–45 mmHg was as a reference, TWA-$PaCO_2$ < 35 mmHg (OR 2.15[95 % CI 0.83–5.55], $P = 0.113$) and TWA-$PaCO_2$ > 45 mmHg (OR 8.31[95%CI

Table 1
Clinical characteristics.

Characteristic	mRs 0–2 (n = 110)	mRs 3–6 (n = 49)	P
Age, year	50.8 ± 9.6	57.7 ± 10.4	<0.001
Sex, female	58(52.7 %)	27(55.1 %)	0.782
BMI, kg/m^2	24.7[22.5–26.1]	24.7[23.3–27.3]	0.392
History of hypertension	60(54.5 %)	27(55.1 %)	0.948
History of diabetes	5(4.5 %)	6(12.2 %)	0.077
History of cardiovascular disease	4(3.6 %)	2(4.1 %)	1.000
Tobacco use	16(14.5 %)	7(14.3 %)	0.966
Alcohol use	13(11.8 %)	8(16.3 %)	0.438
Location of responsible aneurysm			0.816
Middle cerebral artery	38(34.5 %)	17(34.7 %)	
Anterior communication artery	38(34.5 %)	16(32.7 %)	
Internal carotid artery	13(11.8 %)	9(18.4 %)	
Posterior communication artery	10(9.1 %)	5(10.2 %)	
Anterior cerebral artery	6(5.5 %)	1(2.0 %)	
Other	5(4.5 %)	1(2.0 %)	
Time from onset to admission, day	2 [1–3]	2 [1–3]	0.653
Left lateral of responsible aneurysm	51(46.4 %)	26(53.1 %)	0.435
More than one aneurysm	15(13.6 %)	8(16.7)	0.619
Hunt-Hess grade 3-5	35(31.8 %)	34(69.4 %)	<0.001
Modified Fisher scale 3-4	57(51.8 %)	41(83.7 %)	<0.001
Opioids	40(36.4 %)	30(61.2 %)	0.004
Mechanical Ventilation	19(17.3 %)	34(69.4 %)	<0.001
TWA-$PaCO_2$			0.024
TWA-$PaCO_2$ < 35 mmHg	47(42.7 %)	25(51.0 %)	
TWA-$PaCO_2$ 35–45 mmHg	62(56.4 %)	20(40.8 %)	
TWA-$PaCO_2$ > 45 mmHg	1(0.9 %)	4(8.2 %)	

Data are shown as mean ± standard deviation or median [interquartile range] or number (percentage); mRs, modified Rankin scale; BMI, body mass index; TWA-$PaCO_2$, time-weighted average-arterial partial pressure of carbon dioxide.

Table 2
Multivariate logistic regression analysis for unfavorable neurological outcome.

Variables	Adjusted OR [95 % CI]	P
Age	1.06[1.02–1.11]	0.008
Hunt-Hess grade 3-5	1.55[0.61–3.94]	0.360
Modified Fisher scale 3-4	4.02[1.39–11.66]	0.010
Opioids	1.47[0.50–4.29]	0.482
Mechanical ventilation	7.23[2.61–20.00]	<0.001
TWA$PaCO_2$		0.116
TWA-$PaCO_2$ < 35 mmHg	2.15[0.83–5.55]	0.113
TWA-$PaCO_2$ 35–45 mmHg	Reference	
TWA-$PaCO_2$ > 45 mmHg	8.31[0.72–96.14]	0.090

OR, odds ratio; CI, confidence interval; TWA-$PaCO_2$, time-weighted average-arterial partial pressure of carbon dioxide.

0.72–96.14], P = 0.090) were not shown to be an independent risk factor for unfavorable neurological outcomes.

3.3. Nonlinear relationship between $PaCO_2$ and unfavorable neurological outcomes

We conducted a restricted cubic spline to show the nonlinear relationship between TWA-$PaCO_2$ as a continuous variable and unfavorable neurological outcome (defined as an mRs score of 3–6) (Fig. 3). After adjusting the confounders, including age, Hunt-Hess grade, modified Fisher scale, mechanical ventilation, and opioids, the relationship was shown as a "U" shape curve, with the P value

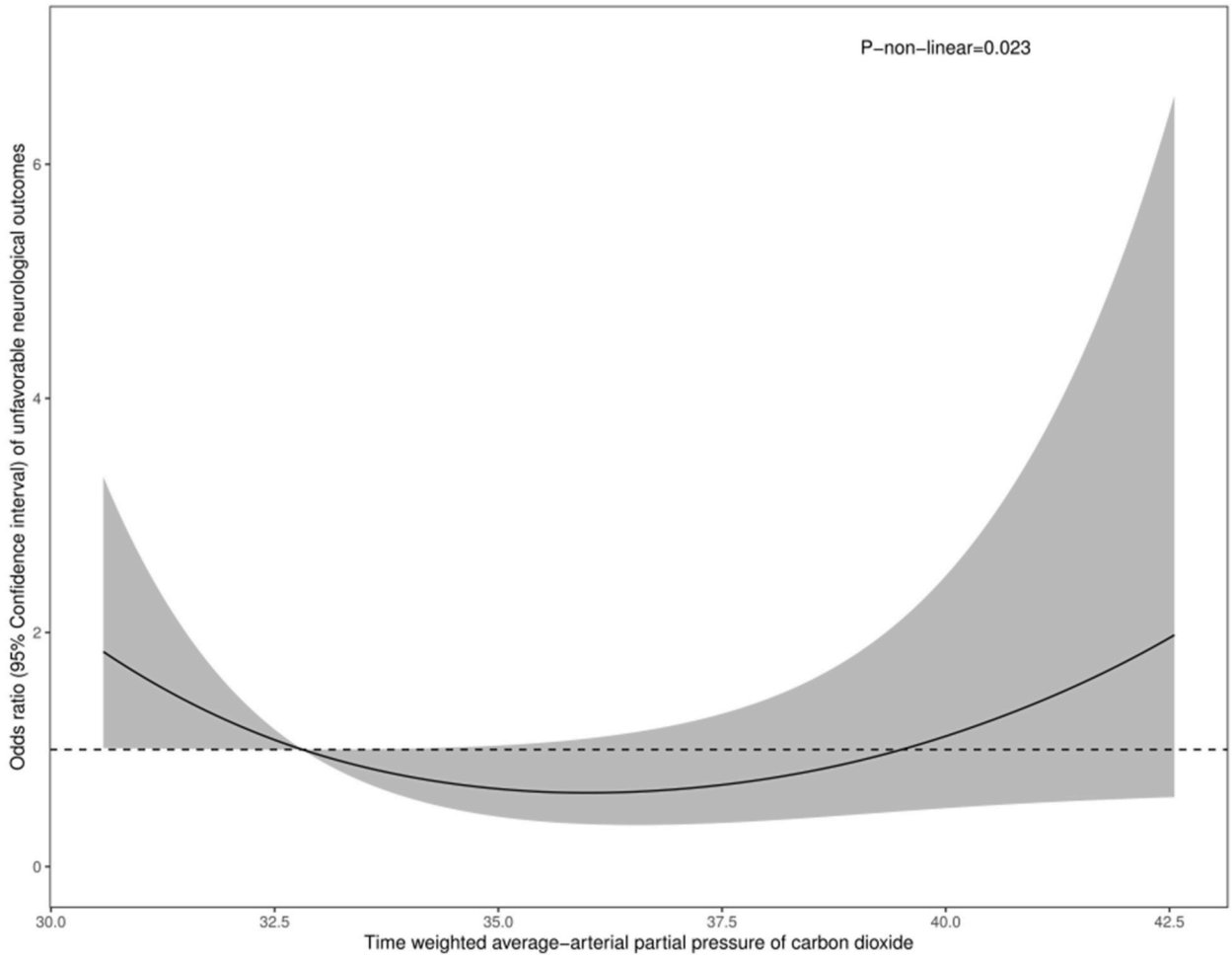

Fig. 3. The restricted cubic spline shows the nonlinear relationship between TWA-$PaCO_2$ levels and unfavorable neurological outcomes in aSAH patients. The nonlinear P-value is 0.023.

0.023 indicating a nonlinear relationship between $PaCO_2$ levels and unfavorable neurological outcomes, and the lowest range was within 32.8–38.1 mmHg. TWA-$PaCO_2$ levels lower than 32.8 mmHg or higher than 38.1 mmHg were associated with an increasing odds ratio of unfavorable neurological outcomes.

4. Discussion

This study explores the associations between dynamic $PaCO_2$ levels and neurological outcomes in aSAH patients. We found that both lower and higher $PaCO_2$ levels are harmful to aSAH patients. The optimal $PaCO_2$ range was within a narrower range (32.8–38.1 mmHg) for aSAH patients sampled in our study.

In physiology, $PaCO_2$ levels mainly depend on production and elimination [6] and fluctuate within 35–45 mmHg [14]. Nevertheless, higher and lower $PaCO_2$ levels were quite common in clinical scenarios. In addition, CO_2 can freely diffuse across the blood-brain barrier [15] to affect the perivascular pH in the brain.

When too much CO_2 is eliminated, $PaCO_2$ levels will decrease. The changes may constrict cerebral small vessels and reduce CBF, accompanied by decreased ICP [16]. According to this, induced hyperventilation was used to interfere with the elevated ICP [17]. Additionally, vasoconstriction has been shown to help restore cerebral autoregulation [18]. However, when CBF reduction reaches the threshold value (3 % for every one mmHg decrease in $PaCO_2$) [3], cerebral ischemic injury worsens [19]. Thus, prophylactic hyperventilation was not advised in cases of brain injury [20]. Vasodilation occurs with increasing $PaCO_2$ levels, with an approximate 2–4% increment in CBF for every unit increase in $PaCO_2$ [21]. Studies have found that CBF increased gradually without raising ICP as $PaCO_2$ levels rose from 30 mmHg to 40, 50, and 60 mmHg [22].

As for the probable mechanisms for CO_2-mediated changes in cerebral vascular tone: altered extracellular pH secondary to $PaCO_2$ changes is the initial step, then neuronal isoform of nitric oxide synthase (nNOS) activates which increases the NO production and cyclic guanosine monophosphate (cGMP) concentration in vascular smooth muscle (VSM). Both NO and cGMP can activate potassium channels, which hyperpolarize VSM. Membrane hyperpolarization inhibits voltage-gated calcium channels, which reduces VSM intracellular calcium concentrations and causes vascular relation [23]. CVS (cerebral vasospasm) can be regarded as an abnormal and prolonged contraction of VSM, which intracellular free calcium level plays a pivotal role in the regulation of smooth muscle contractility [24]. According to Lucke-Wold B et al., a crucial component in the development of vasospasm and subsequent DCI is an increased inflammatory cascade mediated by interleukin (IL-6) [25]. It is interesting how IL-6 levels change in response to CO_2 fluctuations. However, little is known about the association between CO_2 and inflammatory cascade, primarily concerning IL-6, which needs to be investigated in the future. Total expression of NOS enzymes decreases after SAH [26] and free heme molecules from extravasated blood affect NO bioavailability according to Motwani K et al. [27] The pathological changes above will affect the way in which CO_2 dilates cerebral arterioles. Recent data is emerging that glymphatic blockage can increase the inflammatory milieu and cause microspasm. However, little is known about how glymphatic blockage would affect the effect of CO_2 on cerebral vascular tone, which needs further investigation.

Increased or decreased $PaCO_2$ levels affect brain physiology by the mechanisms described above. As for clinical outcomes, some retrospective studies have demonstrated an association between decreased $PaCO_2$ levels and poor neurological outcomes after brain injury. As Williamson et al. [7] reported, $PaCO_2 < 35$ mmHg and $pH > 7.45$ were associated with poor neurological outcomes at discharge. Additionally, several studies found that increased $PaCO_2$ levels were associated with unfavorable outcomes in SAH patients [4,20,28]. According to those, we could learn that decreased or increased $PaCO_2$ levels are not beneficial to clinical outcomes, and the definition of "abnormal" $PaCO_2$ levels among studies varied widely. As of yet, no "optimum $PaCO_2$ levels" have been established for SAH patients in the prospective study, and it has also not been confirmed that maintenance within the range of "optimum $PaCO_2$ levels" can benefit clinical outcomes.

Furthermore, Solaiman et al. found that a longer-lasting hypocapnia was independently associated with poor neurological outcome [9], suggesting that the duration time of abnormal $PaCO_2$ levels should be considered. Clinicians routinely adjust the ventilator settings or sedation levels when $PaCO_2$ values are outside the desired range. Considering only one abnormal $PaCO_2$ value would ignore the effect of duration time of "abnormal" $PaCO_2$ levels and underestimate the impact of clinical interventions. To provide a dynamic CO_2 exposure indicator that takes the duration time of abnormal CO_2 levels into consideration, we calculated the TWA-$PaCO_2$.

Bedside physiology is crucial in the ICU in guiding clinical decision-making [29,30]. Deranged physiology is frequently associated with poor clinical outcomes. Therefore, it is tempting to assume that intervening in physiological parameters might improve patient outcomes [31]. We found the optimal $PaCO_2$ levels for aSAH patients sampled in our study were within a narrow range of 32.8–38.1 mmHg. If we set the target range of 35–45 mmHg, which is a physiological range that may not be ideal for SAH patients. Furthermore, whether fluctuations in $PaCO_2$ levels adaptive or maladaptive in critically ill patients? Further studies should determine if "hypocapnia" or "hypercapnia" represents a disease that requires treatment or if it is a beneficial compensatory response orchestrated by the human body to optimize chances of survival should not be intervened.

Opioids, including fentanyl or remifentanil, were used in 70 (44.0 %) patients in our study. Studies have indicated that opioids have the potential to reduce respiratory rate and minute ventilation in a dose-dependent manner [32,33], leading to an increase in $PaCO_2$ levels. As part of our unit's clinical routine, opioids were administered to relieve pain or intervene in abnormal $PaCO_2$ levels. Accordingly, the use of opioids may be a therapeutic intervention for abnormal $PaCO_2$ levels. Nevertheless, as a retrospective study, we are unable to verify that the purpose of opioid administration or dose adjustments was to control $PaCO_2$ levels. Prospective studies are needed to investigate the effect of opioid usage on abnormal $PaCO_2$ levels and clinical outcomes.

Cerebral injury is one of the most prevalent causes of mechanical ventilation in critically ill patients [34], and ventilatory support is often titrated based on physiological measurements, such as $PaCO_2$ levels. Our study shows that patients with unfavorable outcomes

are more likely to require mechanical ventilation (69.4 % vs. 17.3 %). Still, prospective research needs to investigate if mechanical ventilation in aSAH patients significantly influences $PaCO_2$ levels and clinical outcomes.

There were several limitations in our study. First, studies have shown that patients with cerebral injuries start artificial ventilation in pre-hospital or emergency department settings [35] which time abnormal $PaCO_2$ levels relate to higher mortality [36]. Nevertheless, before ICU admission, $PaCO_2$ measurements could not be obtained for our study. Second, we only enrolled patients who had undergone neurosurgical clipping for intracranial ruptured aneurysms within 24 h after hospital admission. Therefore, generalizing our results to all patients, including elective neurosurgical clipping and neurosurgical clipping for unruptured aneurysms, may be challenging. Third, clinicians might adjust ventilator settings, sedation levels, or other therapies in response to abnormal $PaCO_2$ levels, whether achievement of target $PaCO_2$ levels might be ensured by repeat blood gas analysis. However, ABG data following relevant interventions could not be documented due to the retrospective nature of our study.

5. Conclusion

Our study demonstrates that both lower and higher $PaCO_2$ levels are associated with unfavorable neurological outcomes in aSAH patients. $PaCO_2$ levels within 32.8–38.1 mmHg might be optimal for SAH patients sampled in our study. Prospective studies are still needed to determine an optimal $PaCO_2$ range for SAH patients. Whether an intervention to control $PaCO_2$ levels in aSAH patients benefits clinical outcomes should be explored.

CRediT authorship contribution statement

Rui Su: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Hong-Liang Li:** Methodology, Conceptualization. **Yu-Mei Wang:** Methodology, Conceptualization. **Linlin Zhang:** Writing – review & editing, Methodology, Conceptualization. **Jian-Xin Zhou:** Methodology, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

The study was reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated with Capital Medical University (KY2022-143-01). Because the study was a retrospective nature study. It was allowed to be conducted by board without patients' consent.

Data availability statement

The data supporting the findings of this study are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

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